AMENDMENTS TO THE CLAIMS:

1. (Currently amended) A conjugate of (1) at least one therapeutic agent for joint diseases and (2) hyaluronic acid, a hyaluronic acid derivative or a salt thereof, wherein said at least one therapeutic agent for joint diseases covalently binds to the hyaluronic acid, the hyaluronic acid derivative or the salt thereof via a spacer.

2. (Canceled)

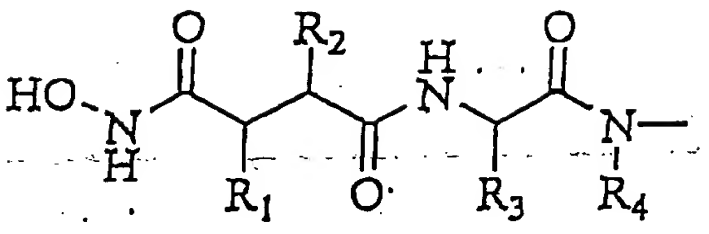
3. (Previously amended) The conjugate of claim 1, wherein the therapeutic agent for joint diseases is a matrix metalloprotease inhibitor.

4. (Canceled)

5. (Previously amended) The conjugate of claim 3, wherein the weight ratio of the matrix metalloprotease inhibitor to the entire conjugate is 0.01 to 50%.

6. (Previously amended) The conjugate of claim 3, wherein the matrix metalloprotease inhibitor is a hydroxamic acid residue.

7. (Previously amended) The conjugate of claim 3, wherein the matrix metalloprotease inhibitor is a hydroxamic acid residue represented by the general formula (1):



(1)

wherein

R_1 is a hydrogen atom, a hydroxyl group or a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

R_2 is a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

R_3 is a straight chain or branched alkyl group having 1 to 8 carbon atoms which may be substituted with a cycloalkyl group, an aryl group or a heterocyclic group; and

R_4 is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms.

C1 contd

8. (Currently amended) The conjugate of claim ~~4~~ 1, wherein the spacer is represented by the general formula (2):

$$-R_5-R_6-R_7-R_8- \qquad (2)$$

wherein

R_5 is a straight-chain or branched-chain alkylene group having 1 to 8 carbon atoms;

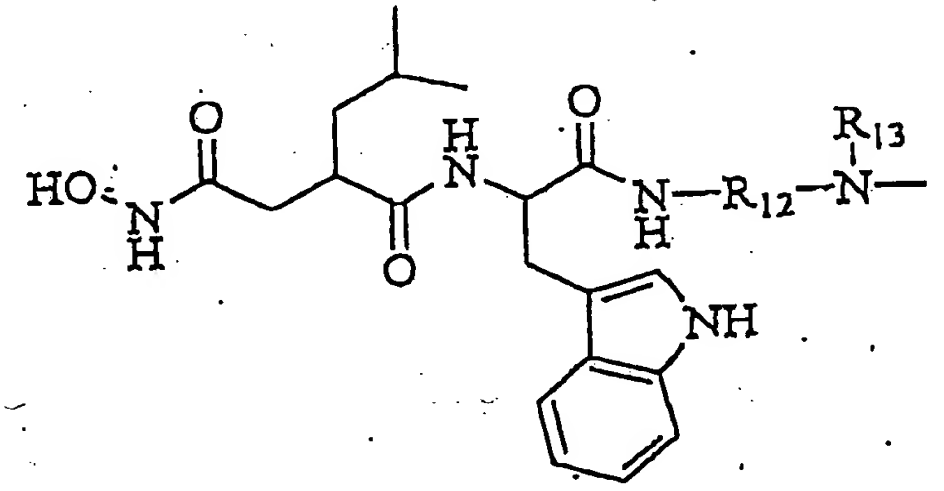
R_6 is an oxygen atom or a methylene or imino group which may be substituted with a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;

R_7 is a straight-chain or branched-chain alkylene group having 1 to 10 carbon atoms into which one to three oxygen atoms may be inserted; and

R_8 is an oxygen atom, a sulfur atom or NR_9 wherein R_9 is a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms.

9. (Currently amended) The conjugate of claim ~~4~~ 1, wherein the ~~conjugate of the~~ matrix metalloprotease inhibitor and the spacer constitute a moiety ~~is~~ represented by the general formula (3):

C1 contd



(3)

wherein

R_{12} is a straight-chain or branched-chain alkylene group having 2 to 23 carbon atoms into which one imino group and/or one to four oxygen atoms may be inserted; and

R_{13} is a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms.

10. (Previously amended) The conjugate of claim 3, wherein the matrix metalloprotease inhibitor in the form of a conjugate with hyaluronic acid, a hyaluronic acid derivative or a salt thereof inhibits a matrix metalloprotease *in situ*.

11. (Previously amended) A method for preparing the conjugate of claim 1 comprising binding a site of the therapeutic agent for joint diseases that does not affect the activity of the agent to a carboxyl group, a hydroxyl group or a functional group at the reducing end of hyaluronic acid, a hyaluronic acid derivative or a salt thereof by direct chemical reaction or via a spacer.

C1 Cont'd

12. (Currently amended) A pharmaceutical composition comprising the conjugate of <u>any one of claims 1, 3, 5-10, 18-21, 23 and 24 and a pharmaceutically acceptable diluent.</u>

13. (Original) The pharmaceutical composition of claim 12 which is a therapeutic agent for joint disease.

14. (Original) The pharmaceutical composition of claim 13, wherein the joint disease is osteoarthritis, rheumatoid arthritis or scapulohumeral periarthritis.

Claims 15 and 16 (cancelled)

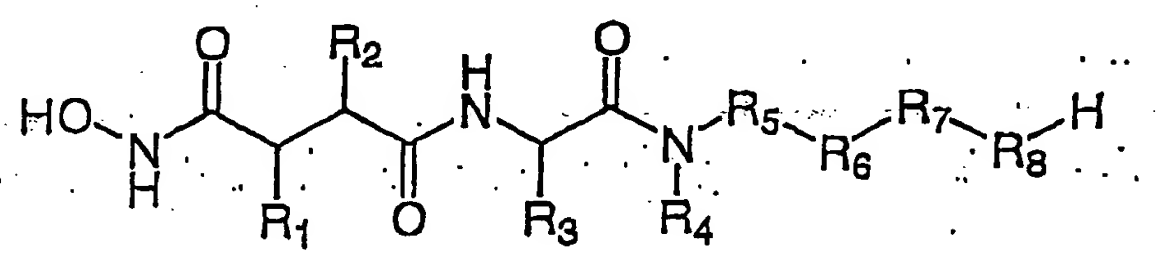
17. (Currently amended)A method for treating a patient having a joint disease comprising administering a pharmaceutical composition containing a pharmaceutically effective amount of the conjugate of ~~claim 1~~ any one of claims 1, 3, 5-10, 18-21, 23 and 24 as the effective ingredient to the patient.

18. (Previously added) The conjugate of claim 1, wherein the therapeutic agent for joint diseases is selected from the group consisting of a cyclooxygenase 2 inhibitor, an antirheumatic agent and a matrix metalloprotease inhibitor.

19. (Previously added) The conjugate of claim 1, wherein the bond between at least one therapeutic agent for joint diseases and hyaluronic acid, a hyaluronic acid derivative or a salt thereof is selected from the group consisting of an amide bond, an ether bond and a sulfide bond.

C1 contd

20. (Currently amended) A conjugate obtained by reacting a compound represented by the following general formula:



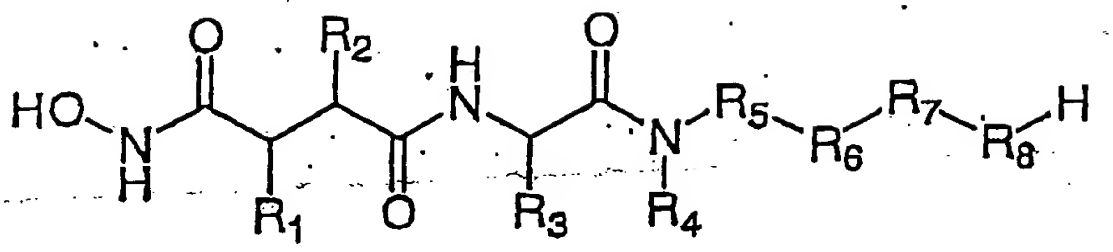
wherein

R_1 is a hydrogen atom, a hydroxyl group or a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;
R_2 is a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;
R_3 is a straight chain or branched alkyl group having 1 to 8 carbon atoms which may be substituted with a cycloalkyl group, an aryl group or a heterocyclic group;
R_4 is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms;
R_5 is a straight-chain or branched-chain alkylene group having 1 to 8 carbon atoms;
R_6 is an oxygen atom or a methylene or imino group which may be substituted with a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;
R_7 is a straight-chain or branched-chain alkylene group having 1 to 10 carbon atoms into which one to three oxygen atoms may be inserted; and
R_8 is an oxygen atom, a sulfur atom or NR_9 wherein R_9 is a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;

C1 contd

with hyaluronic acid, a hyaluronic acid derivative or a salt thereof and a dehydrative condensation agent.

21. (Currently amended) A conjugate according to claim 20 obtained by reacting a compound represented by the following general formula:



wherein

R_1 is a hydrogen atom, a hydroxyl group or a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

R_2 is a straight-chain or branched-chain alkyl group having 1 to 8 carbon atoms;

R_3 is a straight chain or branched alkyl group having 1 to 8 carbon atoms which may be substituted with a cycloalkyl group, an aryl group or a heterocyclic group;

R_4 is a hydrogen atom or an alkyl group having 1 to 4 carbon atoms;

R_5 is a straight-chain or branched-chain alkylene group having 1 to 8 carbon atoms;

R_6 is an oxygen atom or a methylene or imino group which may be substituted with a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;

R_7 is a straight-chain or branched-chain alkylene group having 1 to 10 carbon atoms into which one to three oxygen atoms may be inserted; and

R_8 is an oxygen atom, a sulfur atom or NR_9 wherein R_9 is a hydrogen atom or a straight-chain or branched-chain alkyl group having 1 to 4 carbon atoms;

with hyaluronic acid, a hyaluronic acid derivative or a salt thereof, a dehydrative condensation agent and a reaction accelerating additive.

22. (Currently amended) ~~In a~~ A method of treating a joint disease in a patient in need thereof, comprising administering a pharmaceutical composition to said patient in an amount sufficient for said treatment, ~~the improvement~~ wherein said pharmaceutical composition comprises a conjugate in accordance with claim ~~4~~ 1.

23. (New) The conjugate of claim 1, wherein component (1) is a single therapeutic agent for joint disease.

concld

24. (New) The conjugate of claim 1, wherein component (2) is hyaluronic acid or a salt thereof.